REMARKS

Claim 21 has been amended to correct clerical and grammatical errors and to better claim the invention. The recitation of purity is supported by the as-filed application, for example, at page 17, lines 10-15. Claim 25 has been amended to better claim the subject matter Applicants regard as their invention. Claims 21-25 remain in this application. None of the amendments made herein constitutes the addition of new matter.

The Prior Art Rejections

Claims 21, 22 and 24 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Takao et al. (1996). Applicants respectfully traverse this rejection.

The Patent Office has alleged that SEQ ID NO:2, amino acids 230-828, is taught at Fig. 2 (pg. 1269) and the incision assay for double-stranded DNA is described at page 1268.

The methods of claims 21, 22 and 24 relate to UV damage endonuclease proteins which are truncated, stable, and are capable of effecting enzymatic activity related to DNA damage repair. Claims 21 and 23 have been amended to recite SEQ ID NO:6 (the GST tail fused to the truncated UVDE protein) rather than SEQ ID NO:2, which is the GST tail fused to the full length UVDE protein. Importantly, and surprisingly, the truncated Uve1p proteins or Uvelp fusion proteins of the present invention are stable upon purification and retain enzymatic activity when substantially purified, especially to 90% or greater purity, thus insuring utility of these proteins in DNA repair. The cited reference does not enable the methods of claims 21, 22 and 24 because the cited Takao reference does not teach a truncated Uve1p protein which exhibits stability and high enzymatic activity in a substantially purified state, nor does this response teach fusion

proteins. Rather, the cited reference teaches away from the possibility obtaining a stable truncated Uve1p which could be used in methods for cleaving distorted DNA, as claimed.

A careful reading of the Takao reference reveals that this reference teaches that the truncated endonuclease was not stable in pure form, and that the assays described therein were carried out with endonuclease preparations which were only about 35 % pure (page 1269, column 1). By contrast, the present application teaches that the truncated UVDE proteins were purified to nearly electrophoretic homogeneity and that the proteins made were stable in pure form. The cited reference does not teach a GST-truncated UVDE fusion protein (SEQ ID NO:6), as now recited in claims 21 and 23. Claim 21 specifies that the truncated endonuclease based on SEQ ID NO:4, is purified. Thus, Applicants respectfully submit that the present claimed invention is effectively distinguished over the teachings of the cited Takao reference. The purified endonuclease preparations of the prior art were not stable, as are those taught in the present application. Moreover, the cited reference does not each endonuclease activity on all the types of distorted DNAs as taught in the present case.

Claims 21 and 23, as corrected, recite the use of the endonuclease consisting of the amino acid sequence of SEQ ID NO:6 (GST-truncated Uvelp) for action on UV-irradiated DNA and DNA containing photoproducts causing distortion. SEQ ID NO:6 is not taught by the cited reference. In addition, claims 21 and 22 as amended recite SEQ ID NO:4, the truncated UVeP1 in stable, purified form (at least 90 %). As noted, the reference does not disclose a stable purified enzyme.

The Takao reference does teach a truncated enzyme prepared from recombinant *E. coli*, although it is said not to be stable in purified form. It does not teach that the instability is a result

of the expression host or that stability would be improved in a different recombinant host. The Takao reference does not enable a stable purified truncated UVDE enzyme.

Accordingly, the present invention as now claimed is not anticipated by the cited Takao reference, and the rejection must be withdrawn.

Claim 25 has been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Yajima (1995). Applicants respectfully traverse this rejection.

The Patent Office has alleged that SEQ ID NO:36 is shown in Fig. 2 (pg. 2394) and the two versions of the incision method is taught at page 2399. The cited Yajima reference relates to a UV damage specific endonuclease from *Neurospora crassa*. The first incision assay taught at page 2399 is one in which closed circular plasmid DNA has been UV-irradiated. The second assay is one in which oligonucleotides with the photoproducts of di pyrimidine sites.

Applicants emphasize that claim 25 does not recite photoproducts or UV-irradiated DNA in the method. Accordingly, Applicants respectfully urge that the cited Yajima reference does not anticipate the invention as presently claimed, and the withdrawal of the rejection is requested.

Claim 25 has been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over WO 04626 (Bellacosa et al., 1999). Applicants respectfully traverse this rejection.

The claim is said to be directed to the use of the DNA damage nuclease of SEQ ID NO:38 in a method for cleavage of double stranded DNA characterized by a distorted structure.

Bellacosa is said to teach the cloning, sequencing and characterization of human MED1, SEQ ID NO:38 of the present application. Bellacosa is said to teach endonucleolytic activity against heat damaged calf thymus DNA (denatured), with reference to page 52 and Figure 9. Figure 12 relates to a model in which MED1 cleaves hemimethylated DNA.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claim 25 to add the proviso that the distorted DNA structure is not the result of mismatched nucleotide pairing when the endonuclease comprises the amino acid sequence of SEQ ID NO:38.

With the amendment to claim 25, Applicants respectfully submit that the invention as claimed is not anticipated by the cited Bellacosa reference. Accordingly, the withdrawal of the rejection is respectfully requested.

Claims 21, 23 and 24 have been rejected under 35 U.S.C. 102(b) as allegedly unpatentable over Takao et al. (1996) in view of Ford et al. Applicants respectfully traverse this rejection.

Based on the Examiner's discussion, it is believed that this rejection was meant to be made under 35 U.S.C. 103. Applicants have responded as if the rejection were made under Section 103 rather than 102(b). A supplemental response will be provided if this understanding is incorrect.

The shortcomings of the Takao reference have been discussed above. The reference did not teach or suggest that a stable, purified truncated UVeP1 could be prepared. There is no teaching or suggestion that the recombinant host cell was the source of the instability, as the Patent Office appears to have theorized. Applicants circumvented the problems inherent in the Takao

reference, and have provided to the art the truncated UVeP1 which is stable as an active protein in purified form.

With respect to the mention at page 1271, right column, line 20, of expression of the referenced gene in Saccharomyces, Applicants respectfully maintain on the record that there is no indication that this expressed gene product was purified from the *Saccharomyces* host cell. The context of the paragraph suggests to the undersigned that complementation studies in *Saccharomyces* were carried out. Such studies typically involve intact (live) cells and not purified proteins.

The Patent Office has acknowledged that difficulties in preparing a purified enzyme were reported by Takao. The Patent Office has characterized the cited Ford reference as teaching a fusion protein comprising a GST tail fused to an enzyme of interest. The Patent Office has concluded that it would have been obvious to one of ordinary skill in the art to "have the method of Takao et al and to modify the expression and purification of the UVDE endonuclease as taught by Ford."

The modification is said to come from the Ford reference which states "On a lab scale fusion tail recovery systems are powerful and elegant tools to one-step recovery and purification of recombinant proteins or identification of proteins encoded by cloned cDNAs. On an industrial scale, fusion tail technology can be used in the recovery and purification of both higher-cost pharmaceuticals and lower-to medium-cost enzymes." The Patent Office has alleged that the expectation of success is high because of well-developed and routine use of the GST fusion protein in the art.

Applicants respectfully remind the Patent Office that where references are combined, the motivation for their combination must come from the references themselves. The cited Takao reference does not state the origin of the instability of the truncated enzyme – was it a destructive activity in the recombinant cell extract or was it an inherent property of the truncated enzyme protein? Although the Ford reference states that the GST tail has been used to produce a large number of intracellular target proteins, there is no teaching or suggestion in either of the cited references to combine the GST tail with the truncated UVDE protein to allow purification of the truncated UVDE such that it is stable in purified form. Applicants respectfully note that the Ford reference provides 8 types of tails, including 3 different enzyme-based tails, which had been used in recombinant protein production. Where the truncated UVDE was taught by Takao to be problematic as a purified enzyme, it could not have been more than obvious to try a fusion protein approach to remedy the instability. There is nothing that suggests that this approach, specifically the GST approach, would allow the purification of a truncated UVDE that is stable. Obvious to try is not the proper standard for a conclusion of obviousness (In re O'Farrell, 7 U.S.P.Q.2d 1673 C.A.F.C, 1988).

In view of the foregoing discussion, Applicants respectfully maintain that the cited references do not render obvious the invention as claimed, and that the rejection must be withdrawn.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (one month) and authorization to charge the fee of $55.00 as required by 37 C.F.R. 1.17 to Deposit Account No. 07-1969. It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount authorized is incorrect, however, please charge the correct amount to Deposit Account No. 07-1969.

Respectfully submitted,

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